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13. ABSTRACT (Maximum 200 Words) Surgery for breast cancer includes removal of the breast tumor along with the axillary lymph nodes. The status of these nodes helps clinicians determine prognosis and guides treatment decisions. Unfortunately, a relatively common side effect following axillary lymph node dissection is upper-extremity lymphedema. The purpose of this study is to identify risk factors for lymphedema among women who have had axillary surgery for breast cancer. Specific aims include identifying risk factors for lymphedema and comparing quality of life (QOL) ratings for women who have and do not have lymphedema. A case-control study will be conducted with enrollment of 200 participants. Cases will be identified at their lymphedema consult in the physical therapy centers. Using the oncology registry, controls will include patients who have had breast cancer surgery and have not developed lymphedema. The severity of lymphedema and interference with daily life will be assessed with the Measure of Arm Symptom Survey (MASS), a patient-completed survey, and QOL will be collected with the SF-36. Treatment risk factors including previous surgery, radiotherapy and chemotherapy will be obtained from oncology registry data. This study will determine which factors play a role in lymphedema development.				
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I. Introduction

Lymphedema is a common problem for patients diagnosed with breast cancer, with an estimated 6 – 35% developing it sometime after breast cancer treatment.¹⁻¹⁵ In 2004, it is estimated that 215,990 women will be diagnosed with breast cancer, and 87% of these women will survive at least 5 years.¹⁶ As breast cancer survival rates increase, lymphedema may become a more prevalent problem. The reported incidence varies with the length of follow-up, the measurement techniques, and other patient and treatment-related factors.⁵ It can range from mild to severe, and can be a chronic condition that affects patients' quality of life for years after cancer surgery. Patients are interested in learning how to prevent lymphedema because it is one of the more feared side effects following completion of treatment.

A less invasive procedure, sentinel lymph node dissection (SLND), has shown a reduction in reported lymphedema and other arm symptoms.^{9,22-25} In a study conducted at Park Nicollet Institute, 4.7% of SLND patients reported arm swelling at six months after surgery versus 19.5% of ALND patients ($p < .001$).²² However, patients are not eligible for SLND if they have clinically positive nodes, a pathologically positive sentinel node, or if the surgeon is unable to locate the sentinel lymph node.

Several treatment-related factors have been associated with lymphedema including the extent of axillary dissection, axillary radiation therapy after surgery, type of surgery, and the presence of infection in the ipsilateral arm.^{2-6,12,26-31} Several patient-related factors have also been evaluated for their association with lymphedema in breast cancer patients including body mass index, airline travel, hypertension, diabetes, smoking and age at breast cancer diagnosis, and findings have been inconsistent.^{1,3-5,12,14,15,29,32}

Previous studies have several limitations. Most of the studies have a small sample size without a comparison group, making it difficult to determine which factors are significantly associated with lymphedema. The surgery and treatments for breast cancer have changed in the past two decades, with a higher proportion of patients now having lumpectomies, sentinel lymph node dissections, and adjuvant treatments. Women are advised to avoid lifting weights, constrictive pressure, and activities that could lead to arm injury or infection, but most of this advice is based on very limited data. Therefore, there is a need for additional studies to identify factors that contribute to the development of lymphedema in breast cancer patients.

II. Body

Specific aims. The primary specific aim of this study is to identify risk factors for lymphedema among women who have had axillary surgery for breast cancer. Secondary aims are: 1) to evaluate which factors predict moderate to severe lymphedema in patients who have lymphedema, 2) to describe patients' rating of the interference with daily life caused by lymphedema, 3) to compare the reported quality of life using the SF-36 (Short Form-36) for patients with and without lymphedema, 4) to compare arm circumference measurements to patient-reported lymphedema, and 5) to identify the cause(s) to which patients attribute their lymphedema.

Study design. This study uses a matched case-control design, which permits identification of risk factors that are present more often in lymphedema cases than in controls who have had breast cancer surgery but have not developed lymphedema. Lymphedema cases will be identified at the

time they present to the lymphedema management program in the physical therapy centers at four participating institutions – Park Nicollet Health Services (Methodist Hospital), Fairview-University Medical Center, Fairview Southdale Medical Center, and the Humphrey Cancer Institute. The protocol and consent forms for the study were reviewed and approved by the participating institutional review boards.

Research subjects. Patients are eligible to participate if they have a clinical diagnosis of lymphedema, have had unilateral axillary surgery for invasive breast cancer, have no known metastatic disease present, and are able and willing to give consent. Control participants will be identified using the oncology registry at each institution. Controls will be eligible for the study if they do not have a clinical diagnosis of lymphedema, have had unilateral axillary surgery for invasive breast cancer, have no known metastatic disease present, and are able and willing to give consent. Controls will be matched to cases on date of axillary surgery (within 3 months) and type of axillary dissection (sentinel versus axillary lymph node dissection). Controls will not be matched on age or any other factors because matching on a variable precludes the possibility of assessing its role as a potential risk factor. Using previous literature to estimate effect size, sample size for this study is set at 100 cases and 100 controls.

Questionnaires. The Measure of Arm Symptom Survey (MASS-Version 3) will be administered to cases and controls as a subjective measure of lymphedema. Breast cancer patients with lymphedema (i.e., cases) are asked to complete a revised questionnaire (MASS – Version 3 lymphedema) with questions referencing the date of the onset of arm swelling. Potential lymphedema risk factors are assessed in the MASS including diabetes, hypertension, cigarette smoking, past shoulder injury, flexibility exercises, strength training exercises, medical procedures, arm/hand injury, airline travel, body mass index (BMI) and occupation. The questionnaires address the severity of symptoms by having patients rate them on a 5-point Likert-type scale from no swelling to very severe swelling. The degree of interference with life activities will be assessed using a similar 5-point scale of “not at all” to “very much”. The MOS 36-Item Short-Form Health Survey (SF-36) will be administered to cases and controls to assess general health-related quality of life. This questionnaire uses two summary component scales (physical and mental), and higher scores reflect greater quality of life. To assess test-retest reliability, a second MASS questionnaire will be mailed to the first 20 cases and the first 20 controls in the study within two weeks after the initial questionnaires are completed. After reliability information is collected on 20 cases and 20 controls, the questionnaires will be administered on a one-time basis.

Setting. Patients are being recruited from four lymphedema clinics in Minneapolis, Minnesota and surrounding suburbs. Park Nicollet Health Services (PNHS) is a large multi-specialty clinic with approximately 370 breast cancer cases diagnosed annually. Fairview-University Medical Center (F-UMC) is a National Cancer Institute-designated Comprehensive Cancer Center with approximately 150 breast cancer cases diagnosed annually. Fairview Southdale Medical Center (FSMC) is affiliated with a regional hospital with approximately 300 breast cancer cases diagnosed annually. The Humphrey Cancer Institute (HCI) is affiliated with North Memorial Medical Center, a regional hospital with approximately 320 breast cancer cases diagnosed annually. Adequate numbers of control patients are available because of the large number of breast cancer patients diagnosed annually at each institution.

Data analysis. Univariate analysis will be conducted to describe the characteristics of cases and controls. Chi-square tests will be used to compare cases and controls on potential risk factors for lymphedema. Conditional logistic regression analysis will be used to model the association of potential risk factors with the presence of lymphedema.

III. Key Research Accomplishments

- Preparations to begin the study
 - Determined staff and roles on the study
 - Reviewed and revised MASS instrument with input from the lymphedema education group
 - Presented study and consent forms to 3 IRBs (Fairview IRB is used for both Fairview University and Fairview Southdale sites)
 - Received IRB and Protocol Review Committee approval to begin enrolling research subjects at the four institutions
 - Developed database and data dictionary for the study
- Accrual and data collection
 - Began accrual of participants in December of 2003
 - Between 12/03 and 8/04 a total of 11 participants have been enrolled in the study (4 participants from Methodist Hospital, 3 participants from the Humphrey Cancer Institute, 2 participants from Fairview-University, and 2 participants from Fairview Southdale).
 - Arm measurement have been taken and recorded on all cases
 - Reliability MASS questionnaires were mailed to all enrolled cases within two weeks of enrollment, and 64% have returned the reliability questionnaires.
 - Treatment data has been collected from the medical records on all participants.
- Amendments have been reviewed and approved by the three IRBs for the study
 - Amendment #1 (4/24/03) made administrative changes in the study which clarified eligibility criteria, changed study design to a matched case control design with conditional logistic regression, modified the MASS to version 3.
 - Amendment #2 (10/14/03) revised the subject letter, and made administrative changes in the protocol.
 - Amendment #3 (2/17/04) changed the eligibility criteria from 10% to 5% difference between arms in patient's total arm girth.
 - Amendment #4 (7/9/04) changed the eligibility criteria from 5% to "a clinical diagnosis of lymphedema" and changed the enrollment procedures for controls to absence of a clinical diagnosis of lymphedema.

IV. Reportable Outcomes

- Research training of the candidate
 - Karen Swenson, RN, MS, AOCN completed her coursework requirements for her doctoral program at the University of Minnesota (37 credit hours). She has recently advanced to doctoral candidacy with the completion of the first and second preliminary papers and the oral prelim examination on 9/10/04.

- Enrollment of research participants
 - Enrollment of 11 research participants
 - Completion of SF-36 and MASS questionnaires, with a second set of MASS reliability questionnaires sent to 11 research participants (7 returned).
- Meetings and training with participating sites
 - Quarterly meetings have been conducted at the participating sites to discuss training, enrollment issues, and possible changes in the protocol to improve enrollment at the sites.
 - Several changes have been made in the protocol (Amendments 1 – 4) to improve the enrollment process at the sites, including making changes in the eligibility criteria, revising and further defining the enrollment process, and ongoing training at all of the sites.

V. Conclusions

This research project has provided the candidate with a valuable learning experience in designing and conducting a case-control study. The candidate has successfully completed coursework for the nursing doctoral program and has advanced to candidacy in the program. This grant has provided the candidate with experience in conducting a multi-center breast cancer study, managing the regulatory process, revising and validating the MASS questionnaire, recruiting and enrolling research participants, and collecting questionnaire data from participants.

Enrollment has been slower than projected in the Statement of Work. With the advent of sentinel lymph node dissection for breast cancer surgery in 1999, the rate of lymphedema after breast cancer surgery has decreased considerably. To increase enrollment, revisions have been made in the eligibility criteria, the consent process has been changed to make it easier for sites to enroll participants, and regular meetings have been instituted with all of the sites on a quarterly basis. Another modification in the study includes a plan to decrease the sample size of the study from 400 to 200 matched pairs. The power and minimal effect size with 200 matched pairs have been recalculated and are listed below in Table 1. The revision in sample size decreases the power to detect the estimated effect size of some of the variables, but remains at an acceptable level for the majority of the variables. The revisions listed above are being instituted so that the study can be successfully completed.

The overall goal of this study is to identify modifiable risk factors for lymphedema in patients who have had breast cancer surgery. This is an important area of study because currently there is a lack of research guiding recommendations on precautions for lymphedema prevention. If modifiable risk factors are identified in this study, they will lead to further research by the investigators on the effectiveness of education and other strategies to prevent lymphedema after breast cancer treatment.

Table 1. Revised sample size calculations are based on 100 matched pairs (200 patients). Calculations were made to determine the power to detect the estimated effect size, and the minimal effect size (OR) that the study could detect. Six variables are added, and the minimal effect size is calculated for each variable.

Variable	Estimated Odds Ratio	Power (1- β)	Minimal Detectable Effect (OR)
RT (yes/no) ²⁹	2.85	.91	2.23
Axillary RT (yes/no) ²⁹	6.31	.99	2.30
Infection (yes/no) ²⁹	16.78	.99	2.96
Tumor size (T2,T3,T4 versus T1) ³³	1.78	<.5	2.23
Nodal status (N1,N2,N3 versus N0) ³³	1.82	.55	2.23
Dissection (ALN vs. SLN) ²³	6.74	.99	2.30
Weight (BMI>27.2 vs. \leq 27.2) ²⁹	1.49	<.5	2.23
Tumor location (UO vs. other) ²³	2.19	.76	2.23
Age (>55 vs. \leq 55) ⁶	1.89	.60	2.23
Smoking			2.30
Hypertension			2.30
Diabetes			2.96
Arm/shoulder injury			2.96
Stretching			2.30
Strength training			2.96

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